Increased intraocular pressure is a risk factor for unexplained visual loss during silicone oil endotamponade

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INCREASED INTRAOCULAR PRESSURE IS A RISK FACTOR FOR UNEXPLAINED VISUAL LOSS DURING SILICONE OIL ENDOTAMPONADE

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Purpose: To identify the incidence rate and risk factors for unexplained visual loss associated with silicone oil endotamponade used during primary repair of macula-sparing rhegmatogenous retinal detachments.

Methods: This retrospective cohort study included patients undergoing pars plana vitrectomy for primary surgical repair of macula-sparing rhegmatogenous retinal detachments in whom silicone oil endotamponade was used. The primary outcome measure was the incidence rate of unexplained visual loss and identification of risk factors associated with vision loss.

Results: Of 1,218 eyes undergoing pars plana vitrectomy for primary retinal detachment repair, 44 eyes were included for analysis. In 9 eyes (20%), an unexplained vision loss occurred. Logistic regression identified increased intraocular pressure (IOP) (prospectively defined as IOP readings during silicone oil endotamponade ≥21 mmHg on two consecutive visits or ≥25 mmHg at any time during this period) as significant predictor (odds ratio = 4.9; $P = 0.04$) and a classification tree ranked IOP as the most important variable for vision loss. Incidence rate of vision loss in eyes experiencing IOP increase was 4.5 vision loss events per 1,000 days at risk compared with 1 event per 1,000 days in eyes without IOP increase, yielding an incidence rate ratio of 4.5 (95% confidence interval: 1.1–17.9; $P = 0.02$).

Conclusion: Sufficient control of IOP during silicone oil endotamponade for primary retinal detachment repair is warranted to reduce the probability of vision loss.

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Today, many rhegmatogenous retinal detachments (RRDs) are treated by pars plana vitrectomy (PPV) and gas endotamponade. In some cases such as with associated proliferative vitreoretinopathy (PVR), giant retinal tears (GRT), inferior tear location, or redetachments, silicone oil (SO) is used for an adequate endotamponade.[1–3] Known complications of SO endotamponades are cataract formation, band keratopathy, glaucoma, and SO emulsification,[4,5] although newer formulations seem to carry lower risks of emulsification.[6]

Recently, attention has been directed to another severe SO-related complication that is now reported more and more frequently. A considerable proportion of eyes treated with SO endotamponade for macula-sparing RRDs suffer from a profound unexplained visual loss.[7,8] Recent studies report on incidence rates (IRs) of nearly 30%.[7,8] So far, the only associated risk factor identified was the duration of SO filling.[7]

The aim of this study was to identify the IR, risk factors, and time of occurrence of unexplained visual loss in patients with SO endotamponade.

Methods

Ethics

Ethics Committee approval was obtained from the Local Ethics Committee of the Canton of Zurich. The study adheres to the tenets of the Declaration of Helsinki.

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Patient Data

A retrospective analysis was performed on all eyes that underwent 23-g PPV from 2012 to 2014 at the University Hospital of Zurich. Included were eyes undergoing PPV for macula-sparing retinal detachments with primary SO endotamponade. Exclusion criteria were eyes with macula-involving retinal detachments, redetachments, non-RRDs, and presence of significant vision-inflicting comorbidities (i.e., macular pathologies or anterior segment pathologies), additional buckling surgery, or additional lens-related surgery (lentectomy/phacoemulsification/intraocular lens implantation) during primary PPV.

Preoperative data included age, sex, visual acuity within 24 hours before RRD repair during preoperative examination, presence of GRT, lens status, refractive error (spherical equivalent), type of SO used, and presence and grade of PVR.

Postoperatively (both after initial RRD repair with SO filling and after PPV for SO removal), all patients were seen on the first day after surgery, weekly during the first month and after 1, 2, and 3 months. During each visit (preoperatively and postoperatively), best visual acuity achieved using either glasses and/or pinhole was measured with Snellen charts and transformed to the logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Besides visual acuity, at every visit, intraocular pressure (IOP) and status of the retina were examined. This reflects postoperative routine care for all patients treated at the surgical retina department and allows for a detailed review of the development of vision, IOP, and potential complications during the postoperative period. Intraocular pressure was prospectively defined as increased if IOP readings during SO endotamponade were $\geq$21 mmHg on two consecutive visits, and if IOP was $\geq$25 mmHg at any time during this period.

For all patients, duration of SO endotamponade was calculated. In all patients with a vision loss, optical coherence tomography examination was performed to rule out secondary causes for visual loss (e.g., macular edema, significant epiretinal membrane, and persistent subretinal fluid). Where necessary, a fluorescence angiography was obtained to rule out retinal vascular occlusion. Vision loss was defined as a loss of two or more Snellen lines from baseline visual acuity before RRD repair compared with best-corrected vision after SO removal, with no evident explanation.[7,9]

Outcome Measures

The primary outcome measure was the IR of unexplained visual loss and identification of risk factors associated with vision loss. Secondary outcome measures were time to vision loss, duration of SO endotamponade, and visual acuity and IOP changes.

Statistics

Summary statistics include mean or median and SD or interquartile range (IQR) where appropriate. Exploratory analyses were undertaken with Bayesian logistic regression and classification trees. Candidate risk factors were then used to compute the IR ratio to quantify the relative risks.

All analyses were performed with R version 3.1.3 using the ARM and Rpart packages.

Results

Patients

From 2012 to 2014, a total of 1,218 eyes underwent PPV to treat retinal detachments (Figure 1).

In 248 (20.4%) eyes, SO endotamponade was needed because of the presence of GRT, inferior tear location, and significant PVR. Macula-involving RRDs were seen in 167 eyes; in 13 eyes, a redetachment was present after previous surgeries were performed elsewhere. In nine eyes, SO was used in the treatment of primary retinal detachments in the setting of endophthalmitis (n = 2), acute retinal necrosis (n = 2), extensive peripheral tractional retinal detachment due to toxoplasmosis (n = 1), traumatic detachment (n = 1), peripheral traction detachment secondary to tuberculosis (n = 1), congenital glaucoma surgery (n = 1), and neovascular age-related macular degeneration with extensive subretinal exudation and hemorrhage (n = 1). Overall, 59 primary macula-on RRDs were treated with SO endotamponade. After exclusion of 6 eyes, which were lost to follow-up (tourists who needed to fly back home), and 9 eyes with an explained visual loss (macula-involving redetachment under SO endotamponade in Stickler syndrome n = 5, intraoperative macular damage n = 1, dense cataract n = 1, and toxic macular damage n = 1), a total of 44 patients remained for final analysis (Figure 1). None of the patients with an unexplained visual loss showed macular edema or a thinning of the central retina on optical coherence tomography cross-sections.

As stated, all patients were followed-up routinely on the first day after the operation, weekly during the first month and after 1, 2, and 3 months allowing for a detailed documentation of the course of IOP and visual acuity. Characteristics of eyes with and without unexplained visual loss are shown in Table 1.

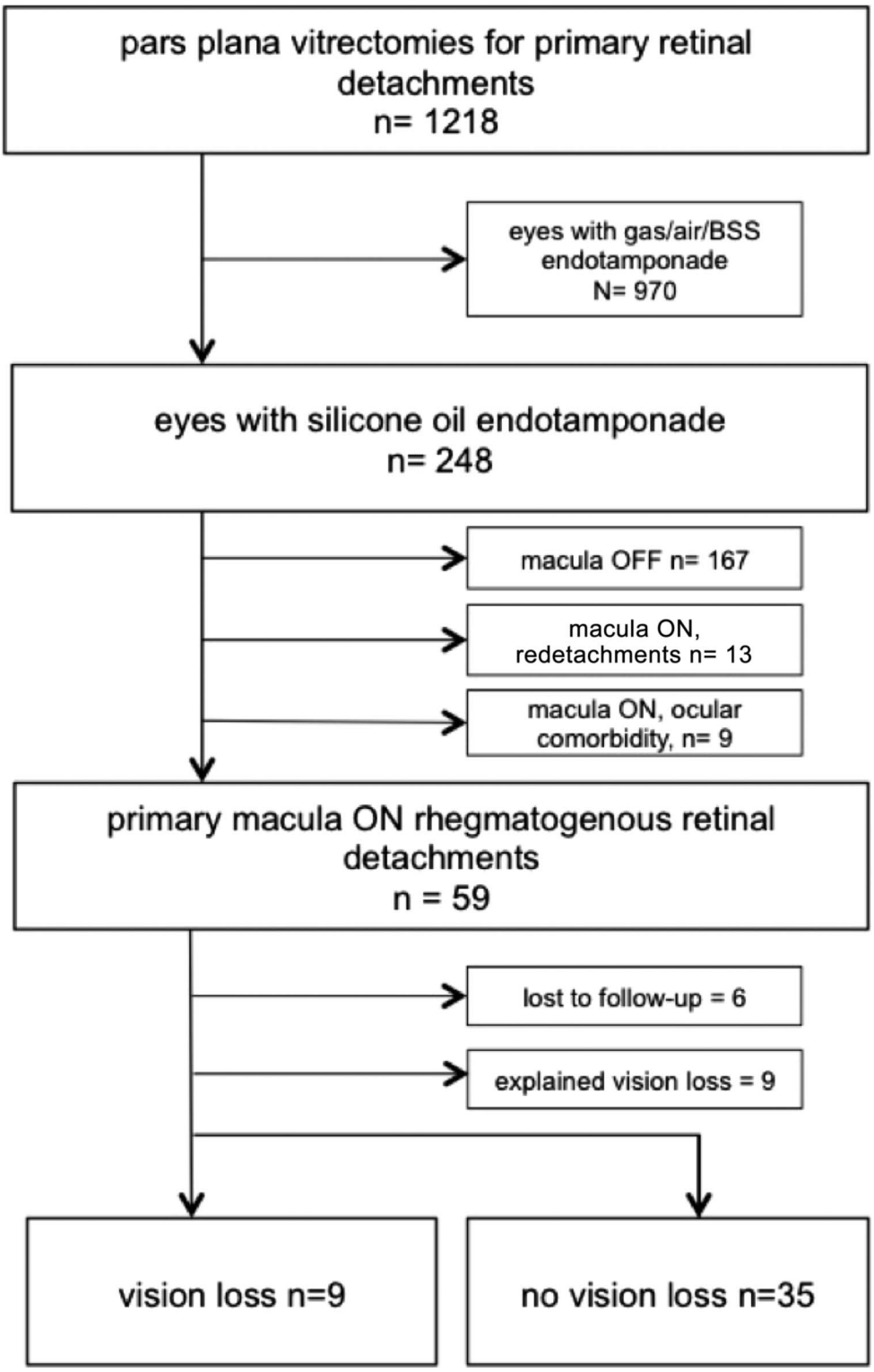

Fig. 1. Flowchart for identification of eligible eyes for final analysis.

Primary Outcome Measures

An unexplained visual loss was found in 9 of 44 patients (20%, Figure 2). Initial exploratory analyses identified increased IOP as a clear safety signal.

Among eyes with recorded increased IOP, median time to increased IOP, as defined above, was 10.2 days [IQR: 1–14 days]. The IR of vision loss in eyes experiencing IOP increase was 4.5 vision loss events

Table 1. Overview of Demographics and Ocular Findings Before PPV

	No Vision Loss	Vision Loss	*P*
N	35	9	
Age, mean (SD)	57.2 (10.87)	54.8 (6.42)	0.532
Sex, %			1.0
Female	7 (20)	2 (22.5)	
Male	28 (80)	8 (77.5)	
Myopia, %			0.1
0 to −3 dpt	20 (57.15)	4 (44.5)	
−3 to −6 dpt	8 (22.85)	5 (55.5)	
More than −6 dpt	7 (20)		
Pseudophakia, %			1.0
Yes	10 (28.5)	2 (22.2)	
No	25 (71.5)	7 (78.8)	
GRT	13 (36.1)	2 (22.5)	0.695
PVR, %			0.575
No PVR	15 (42.9)	6 (66.7)	
Grade A	4 (11.4)	1 (11.1)	
Grade B	11 (31.4)	1 (11.1)	
Grade C	5 (14.3)	1 (11.1)	
SO type, %			0.712
1,000 ct	13 (37)	3 (33.33)	
1,300 ct	20 (57)	6 (66.66)	
5,000 ct	2 (6)		

ct, centistokes; dpt, diopters of spherical equivalent.

per 1,000 days at risk (6/1,334) compared with 1 event per 1,000 days (3/2,993) in the other eyes (i.e., without IOP increase) yielding an IR ratio of 4.5 (95% confidence interval: 1.1–17.9; $P = 0.020$). Thirty-eight percent (6/16) of eyes with increased IOP experienced visual loss compared with 10.7% (3/28) of the remaining eyes. Logistic regression identified IOP as the most important predictor (odds ratio = 4.9; $P = 0.044$), and a classification tree ranked IOP as the most important variable.

Secondary Outcome

Comparison of eyes with and without visual loss showed no evident differences regarding age, sex, refractive error, rate of GRT, and presence and grade of PVR.

Median visual acuity dropped from 20/25 (logMAR 0.1, IQR: 0.1–0.1) preoperatively to 20/125 (logMAR 0.8, IQR: 0.7–1.3) ($P < 0.001$) in the unexplained vision loss group. In eyes without visual loss, vision remained stable at 20/32 (logMAR 0.2, IQR: 0.1–0.4) preoperatively to 20/32 (logMAR 0.2, IQR: 0–0.3) postoperatively.

Preoperative visual acuity in the group without vision loss was lower due to 3 patients with vitreous hemorrhage. In all patients, vision loss occurred during SO endotamponade, documented during regular clinical follow-up. Median vision loss occurred at 108 days (IQR: 60–120 days) days after SO endotamponade. Mean duration of SO filling in the group with vision loss was 161.0 ± 38.8 days and significantly longer as compared with 104.6 ± 43.6 days ($P < 0.001$) in eyes without vision loss. Mean maximal IOP in eyes with vision loss was 26 ± 9 mmHg, whereas in eyes without vision loss, the mean maximal IOP was only 21 ± 7 mmHg ($P = 0.1$).

Discussion

This study in primary macula-on RRDs requiring SO endotamponade found an IR of an unexplained visual loss of 20.5% and increased IOP during SO endotamponade as the most important risk factor to develop vision loss. Furthermore, all events of vision loss were found to occur during SO endotamponade.

The most relevant risk factor for developing unexplained visual loss was an increased IOP during SO endotamponade: events of increased IOP were observed more often in eyes developing vision loss. Although the duration of SO endotamponade was longer in eyes with vision loss, regression analysis did not identify duration of SO endotamponade as a risk factor—which is in contrast to a recent study, where duration of SO endotamponade was associated with an unexplained visual loss.[7] Other variables such as age, sex, lens status, degree of myopia, significant PVR, and presence of GRT were not associated with vision loss.

Until now, the only risk factor described is duration of SO endotamponade.[7] The authors, who presented data on 11 patients with an unexplained visual loss, did not find an effect of IOP elevation. In contrast to the current analysis, they compared the median of the highest IOP during SO tamponade of affected (vision loss) and unaffected eyes. Taking a closer look at the data shows that 8 of 11 (73%) affected patients showed IOP spikes exceeding 25 mmHg supporting our finding that IOP elevations are related to unexplained visual loss. It may be possible that not only the highest IOP is relevant for developing unexplained visual loss but also an increased IOP during a certain period.

Many studies describe vision loss to occur during SO endotamponade or after SO removal,[7–9] others reported that vision loss developed during SO endotamponade.[10] In all our patients, vision loss occurred during SO endotamponade. Because of the established postoperative follow-up routine, including control of visual acuity with correction of the refractive change through SO by adding lenses and/or by using a pinhole, we were able to identify the time point of visual loss. In contrast to the actual time of the vision loss, most

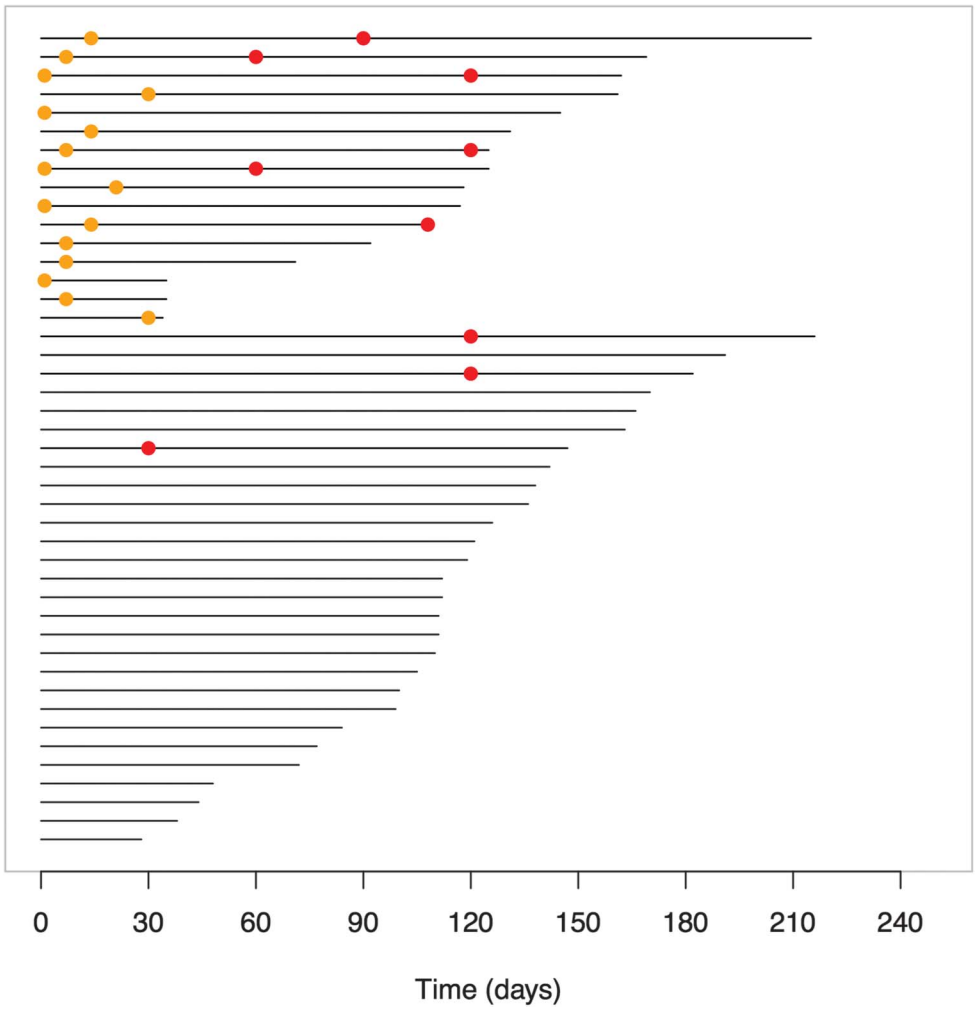

Fig. 2. Events of vision loss are depicted as a red dot and events of increased IOP are a yellow dot. All instances of increased IOP occurred between 1 and 30 days. Instances of vision loss occurred between 30 and 120 days. Thirty-eight percent (6/16) of eyes with increased IOP experienced visual loss. All instances of increased IOP preceded associated instances of vision loss. Black lines visualize time in days since SO endotamponade.

patients only realized the vision loss after SO removal and after resorption of the gas or air bubble instilled during SO removal. Because visual acuity under SO endotamponade may not regularly be examined in routine practice, and not all patients may realize decreased vision until after removal of SO, it is very well possible that in previous studies an actual vision loss during SO tamponade was mistaken for a vision loss after SO removal. We suggest—in line with previous reports—that unexplained vision loss rather occurs during SO endotamponade.[10]

We found a strong relationship between vision loss and IOP elevation. Intraocular pressure increase always preceded vision loss, which occurred during SO endotamponade and not after SO removal. We believe that insufficient pressure control under SO endotamponade plays a key role in the pathogenesis of unexplained visual loss. Nevertheless, how does an increase in IOP lead to a selective central vision loss, and why do only certain patients with IOP problems experience such a vision loss?

Only recently, a study found a focal severe retinal nerve fiber layer (RNFL) loss of the papillofoveal projection and microcystic macular changes in the inner nuclear layer as pathomorphological correlate suiting the severe central vision loss.[11] All patients were mentioned to have had an increased IOP. As SO has been shown to infiltrate various parts of the eye, such as the anterior chamber angle, iris, ciliary body, retina, preretinal and subretinal membranes as well as the optic nerve, and even up to the lateral ventricles,[12,13] the microcystic changes were discussed to be emulsified oil droplets.[11] However, as the RNFL loss precedes the appearance of the vacuoles and the vacuoles are only located in the inner nuclear layer, this was considered unlikely. The described microcystic changes in the inner nuclear layer together with an RNFL thinning were previously shown in optic nerve diseases such as multiple sclerosis,[14–18] neuromyelitis optica,[19–21] idiopathic optic atrophy,[15] relapsing isolated optic neuritis,[16] comprehensive neuropathy,[22] hereditary optic neuropathy,[16,23] trauma,[16] and Tanzanian endemic optic neuropathy.

Furthermore, they have been shown in eyes with glaucoma.[24] Patients with advanced stages of glaucoma were more frequently affected and showed a worse mean defect slope of visual field suggesting a relationship with insufficient pressure control. The microcystic changes were discussed to occur rather with a localized RNFL thinning, as very severely affected eyes with a mean defect < -15.3 dB and thus a widespread RNFL loss did not show any microcysts. Different pathogenetic mechanisms for the development of microcystic changes in eyes with optic neuropathies and in eyes with glaucoma have been discussed. For optic neuropathies, the most popular is the theory of retrograde transsynaptic degeneration,[25] which is a subject of debate though.[23] Inflammatory processes,[14] Müller cell dysfunction,[18] or vitreomacular traction were discussed[23] as alternative possibilities. For glaucoma patients, who were suggested to have rather localized RNFL defects, at least in part, a mechanical traction was suggested. In patients with unexplained visual loss, the retinal changes were shown to occur localized as well, affecting primarily the papillomacular bundle[11] and leading to a central visual field defect shown in microperimetry.[7] In consideration of these findings and the clear association with IOP problems in our study, a mechanical damage of the nerve fibers under changed biomechanics of the eye after vitrectomy and under SO endotamponade with a consecutive development of microcysts in the inner nuclear layer could be hypothesized. A perfusion-related damage might be an alternate explanation. Pressure spikes may reduce the ocular perfusion pressure leading to a specific damage of highly metabolically active nerve fibers in the papillomacular bundle, which are known to have particularly high adenosine triphosphate (ATP) requirements.[26,27] Furthermore, a mitochondrial insufficiency, as seen in patients with endemic optic neuropathies, could play a vital role,[27] especially in conjunction with IOP elevations. Mitochondrial insufficiency may lead to cell injury and death if compensatory mechanisms like proliferation of mitochondria and axonal transport to the site where ATP production is needed fail.[27] Axoplasmic transport is more energy demanding; the smaller the caliber, the less myelinated the fibers are. Delay in the axonal transport was proposed to lead to a breakdown of the transport system resulting in cell death. Very long and fine, constantly firing fibers with a high metabolic demand, as in the optic nerve, have been shown to be most vulnerable. In patients with SO filling, there are changes in the metabolism, like for instance, elevated potassium levels[28] and changes in the level of cytokines[29] have been described. A resulting mitochondrial insufficiency with damage of the vulnerable fibers in the RNFL of the papillomacular bundle in conjunction with a hindered axoplasmic transport under an elevated IOP is a possible pathogenetic mechanism in the development of unexplained visual loss.

Main strengths of this analysis are the large sample size, the formal risk analysis of visual loss related to SO endotamponade, and the uniform dataset from postoperative follow-up examinations. Visual acuity and IOP were measured at given intervals, and visual acuity was measured using correction.

The limitations of the study are inherent to the retrospective nature, especially lack of a control group where IOP was controlled to remain within normal ranges.

Given the robust dataset and the findings that are in line with previous reports, patients should be advised of visual loss despite a preoperatively attached macula situation and IOP elevations should be treated. As in all of our affected patients, IOP elevations occurred before detection of visual loss, we suppose insufficient IOP control plays a key role in the pathogenesis of unexplained visual loss. The pathophysiology remains unclear. Because of the strong association with IOP elevations, we implemented a strict postoperative pressure management into clinical routine and found that the incidence has markedly dropped since. In 2015 and 2016, no case of unexplained visual loss has occurred at our clinic.

Key words: vision loss, silicone oil, silicone endotamponade, vitrectomy, pars plana vitrectomy.

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